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10/528,709	03/22/2005	Martin Geiser	4-32688A	8902

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application No.	Applicant(s)	
10/528,709	GEISER, MARTIN	
Examiner	**Art Unit**	
David J. Steadman	1656	

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 1-18 are pending in the application.

Election/Restriction

[2] Applicant's election without traverse of Group IV, claims 12-17, drawn to the special technical feature of a method for identifying a ligand or a low molecular weight compound, in the reply filed on 9/26/07, is acknowledged.

[3] Claims 1-11 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on 9/26/07.

Claim to Domestic Priority

[4] Applicant's claim to domestic priority under 35 U.S.C. § 119(e) to US non-provisional application 60/413,704, filed on 9/26/02, is acknowledged.

Information Disclosure Statement

[5] The examiner can find no information disclosure statement (IDS) filed in the instant application. If the examiner has inadvertently overlooked an IDS that has been filed in the instant application, applicant's cooperation is requested in alerting the examiner to this IDS in the response to this Office action.

Specification/Informalities

[6] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: --- Three Dimensional Structure of the Catalytic Domain of ZAP-70 and Method of Use in Identifying Binding Compounds---.

[7] As noted in the prior Office action, in order to perfect sequence compliance, applicant is required to submit a specification amendment directing entry of the substitute sequence listing filed on 9/28/06 into the specification.

[8] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly

the disclosed Table 1 of the specification (beginning at p. 29) containing a list of atomic coordinates representing the disclosure of an amino acid sequence. Applicant should identify this sequence by a proper sequence identifier, either in the drawing itself or in the brief description of the drawing.

Claim Objection(s)

[9] Claims 12 and 15 are objected to as being grammatically incorrect and it is suggested that the conjunction "and" be placed at the end of part (i) of claim 12 and at the end of part (iii) of claim 15.

[10] Claim 13 is objected to as being dependent from non-elected claim 11. It appears claim 13 is intended to depend from claim 12 and in the interest of advancing prosecution, the examiner has interpreted claim 13 as being dependent upon claim 12.

[11] Claim 15 is objected to as being grammatically incorrect in the recitation of "with a candidate ligands" and it is suggested that the noted phrase be amended to recite "with a candidate ligand" OR "with candidate ligands".

[12] Claim 15 is objected to in the recitation of "Volubility" and it is suggested that in order to maintain consistency among the terms of the claim, the first letter of the noted term be lower case rather than upper case.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 (claims 16-17 dependent therefrom) is unclear in the recitation of "Volubility" as the term does not appear to be defined in the specification and the intended meaning of this term is unknown. It is suggested that applicant clarify the meaning of the noted term.

Also, the phrase "such as..." in claim 15 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

MPEP § 2163.II.A.3.(b) states, "when filing an amendment an applicant should show support in the original disclosure for new or amended claims" and "[i]f the originally filed disclosure does not provide support for each claim limitation, or if an element which applicant describes as essential or critical is not claimed, a new or amended claim must be rejected under 35 U.S.C. 112, para. 1, as lacking adequate written description."

The claims are drawn to methods for identifying a ligand or low molecular weight compound that binds to the catalytic domain of ZAP-70 using a genus of 3-D structures of the catalytic domain of ZAP-70 kinase. According to the specification, "said catalytic domain of ZAP-70 kinase comprises the sequence of SEQ ID. No. 2, fragment or homologue thereof" (p. 3, bottom). Also, the specification states indicates that the structural coordinated of Table 1 may be used to generate models of ZAP-70 kinase mutants and variants by, *e.g.,* molecular replacement and homology modeling (*e.g.*, specification at pp. 12-13). As such, the recited "catalytic domain of ZAP-70 kinase" and three dimensional structures thereof have been interpreted as encompassing any mutant or variant of SEQ ID NO:2 and the 3D structure of any mutant or variant thereof, respectively.

The Court of Appeals for the Federal Circuit has held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus

may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the genus of 3-D models of a catalytic domain of ZAP-70 kinase, *i.e.,* a 3-D model of amino acids 331-603 of SEQ ID NO:1 having the structural coordinates of Table 1. Other than this single representative species, the specification fails to disclose any other species of the recited genus, which encompasses widely variant species including any 3-D model of the catalytic domain of ZAP-70 kinase from any source and any mutant or variant thereof.

According to the state of the art at the time of the invention, the use of a homology model in rational drug design was highly unpredictable. For example, the reference of Flower ("Drug Design, Cutting Edge Approaches," Royal Society of Chemistry, Cambridge, UK, 2002), in addressing the use of homology models for identifying lead drugs, discloses "[p]roblems still exist, however: the fitting together of protein domains in a multi-domain protein, the determination of the most likely

conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking - to name only a few" (p. 25, middle). See also the reference of Lambert et al. (US Patent Application Publication 2004/0137518), which teaches, "[p]otential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, ¶[0017]). MPEP 2163 states, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus."

Given the lack of description of a representative number of polynucleotides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[15] Claims 12-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using a 3-D model of the ZAP-70 catalytic domain of amino acids 331-603 of SEQ ID NO:1 having the structural coordinates of Table 1, does not reasonably provide enablement for methods of using all 3-D models of a catalytic domain of ZAP-70 kinase having any structural coordinates as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498,

504, 190 USPQ 214, 219 (CCPA 1976). It is the examiner's position that undue experimentation would be required for a skilled artisan to make and/or use the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims...and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims" (citation omitted) and "[w]hen analyzing the enabled scope of a claim, the teachings of the specification must not be ignored because claims are to be given their broadest reasonable interpretation that is consistent with the specification."

According to the specification, "said catalytic domain of ZAP-70 kinase comprises the sequence of SEQ ID. No. 2, fragment or homologue thereof" (p. 3, bottom). Also, the specification states indicates that the structural coordinates of Table 1 may be used to generate models of ZAP-70 kinase mutants and variants by, *e.g.*, molecular replacement and homology modeling (*e.g.*, specification at pp. 12-13). As such, the recited "catalytic domain of ZAP-70 kinase" and three dimensional structures thereof have been interpreted as encompassing any mutant or variant of SEQ ID NO:2 and the 3D structure of any mutant or variant thereof, respectively.

The enablement provided by the specification is not commensurate with the scope of the claims with regard to the large number of 3D structures of the catalytic domain of ZAP-70 kinase as broadly encompassed by the claims. In this case the disclosure is limited to methods using a 3-D model of the ZAP-70 catalytic domain of amino acids 331-603 of SEQ ID NO:1 having the structural coordinates of Table 1.

The nature of the invention: The invention involves *in silico, i.e.,* performed on a computer, screening of compounds that interact with the catalytic domain of ZAP-70 kinase using structural coordinates, which define the amino acid sequence and three-dimensional atomic positions of the atoms of a polypeptide.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, methods of using a 3-D structure of a polypeptide and generating homology models were known in the prior art. However, while methods of generating homology models of a protein using a set of experimentally determined structure coordinates was known, the use of such homology models in

rational drug design was highly unpredictable, particularly as such models may or may not represent the actual biological conformation of a desired polypeptide, as noted by the references of Flower (*supra*) and Lambert et al. (*supra*).

The lack of guidance and working examples: The specification discloses only a single working example of structural coordinates for use in the claimed methods, *i.e.*, the structural coordinates of Table 1 and fails to provide guidance for using those 3-D structures of the catalytic domain of ZAP-70 kinase polypeptides that do not, *e.g.*, have ZAP-70 tyrosine kinase activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of altering a 3-D structure of a protein *in silico* were known at the time of the invention, it was not routine in the art to create a substantial number of altered 3-D structures as encompassed by the claims without guidance of which of those structures is useful according to the disclosed utility.

Thus, in view of the lack of guidance and working examples provided in the specification, the high level of unpredictability, and the significant amount of experimentation required, undue experimentation would be necessary for a skilled artisan to make and use the claimed invention. As such, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation

left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[16] Claims 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Zhu (US Patent 6,589,758; "Zhu") and Hatada et al. (US Patent 6,251,620; cited in the Office action mailed on 8/31/07; "Hatada") using the legal rationale of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103. See also MPEP §§ 2106.IV.B.1.(b) and 2106.VI regarding determination of whether descriptive material is functional or non-functional. Applicant's attention is directed to "ANNEX 3: Comments of the USPTO, Trilateral Project WM4 Comparative studies in new technologies, Theme: Comparative study on 'protein 3-dimensional (3-D) structure related claims'", Vienna, Austria November 4-8, 2002 at www.trilateral.net/projects/biotechnology/protein_3d/wm4_3d_annex_3.pdf.

The claims are drawn to methods for identifying a ligand or low molecular weight compound that binds to the catalytic domain of ZAP-70 using a 3-D structure of the catalytic domain of ZAP-70 kinase derived from the structural coordinates of Table 1 (claim 12) or using the atomic coordinates of Table 1 to determine the 3-D structure of a ZAP-70 catalytic domain (claim 15).

The reference of Zhu teaches atomic coordinates and 3D models thereof of the kinase domain of an Lck kinase in complex with various kinase inhibitors (column 5), *e.g.*, AMP-PNP and staurosporine, wherein the kinase domain is described as having an ATP binding site (column 5, lines 36-38). Zhu teaches the models can be used for identifying potential ligands, *e.g.*, kinase inhibitors, by screening using computer modeling, *i.e., in silica,* to identify potential ligands that bind to the Lck kinase domain model (columns 17-20), including further refinements to the structure of the potential inhibitor by successive iterations of computer fitting and assaying (column 20, lines 36-40). Zhu teaches the identified ligands can be used to inhibit kinase activity of ZAP-70 (column 20, lines 41-53). The reference of Zhu does not expressly teach a method for identifying potential inhibitors using a ZAP-70 catalytic domain model having structural coordinates of Table 1.

Hatada teaches ZAP-70 is a critical mediator of immune response and blocking ZAP-70 function will lead to immunosuppression (column 1, line 66 to column 2, line 2). Hatada teaches rational design of inhibitors of ZAP-70 can identify potential immunosupressive agents (column 2, lines 10-13). As with Zhu, Hatada teaches

methods of rational drug design. The structural coordinates of Hatada are of an SH2 domain – not a catalytic site – of ZAP-70.

In *Gulack* and *Ngai,* the respective Courts held that nonfunctional descriptive material in a claim does not distinguish the prior art in terms of patentability. The key factor in analyzing the obviousness of these claims over the prior art is the determination that the computer algorithm used to identify compounds that may bind ZAP-70 is a known algorithm and is unmodified. If the difference between the prior art and the claimed invention as a whole is limited to descriptive material stored on or employed by a machine, it is necessary to determine whether the descriptive material is functional descriptive material or nonfunctional descriptive material. In this case, because the ZAP-70 structural coordinates as disclosed in Table 1 do not have a functional relationship with the computer upon which they are stored, the structural coordinates are considered to be non-functional descriptive material and the method uses a known unmodified computer algorithm. Data, which are fed into a known algorithm whose purpose is to compare or modify those data using a series of processing steps, do not impose a change in the processing steps and are thus nonfunctional descriptive material. A method of using a known comparator for its known purpose to compare data sets does not become nonobvious merely because new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that would have otherwise been obvious.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to perform rational drug design as taught by Zhu or Hatada using a

3-D model of the catalytic domain of ZAP-70 having the structural coordinates of Table 1 to identify a potential inhibitor of ZAP-70, synthesize the potential inhibitor, and determine the inhibitory activity of the potential inhibitor on the kinase activity of ZAP-70, wherein only non-functional descriptive material is additionally present in the claims, which, according to *In re Gulack* or *In re Ngai,* do not distinguish the claimed methods from those taught by the combination of Zhu and Hatada. One of ordinary skill in the art would have been motivated to practice the *in silico* screening method of Zhu or Hatada using a 3D model of ZAP-70 catalytic domain having structural coordinates of Table 1 because of the suggestion provided by Hatada. One would have had a reasonable expectation of success for practicing the claimed methods because of the teachings of Zhu and Hatada. Therefore, claims 12-17 would have been obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

[17] Status of the claims:

Claims 1-18 are pending.

Claims 1-11 and 18 are withdrawn from consideration.

Claims 12-17 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Monday to Friday, 7:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached at 571-272-0931. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Steadman/
David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656